

REMARKS

Claims 14-18, 20-31, 33 and 34 are pending. Applicants propose to amend claim 16. Reconsideration of the claims and a withdrawal of all outstanding rejections are requested in view of the following remarks.

35 U.S.C. §112 - Indefiniteness

Claim 16 has been rejected as allegedly indefinite because it recites "using a salt of a carboxylic acid" which may be a mono-, di-, or tri-acid. The Examiner asserts that this expands the independent claim (claim 14) upon which claim 16 depends. Applicants have amended claim 16 to make clear that the salt is that of a mono- or di-carboxylate or mono- or di-carboxylic acid recited in claim 14. This amendment obviates the rejection.

The Examiner has additionally rejected claims 14-18, 20-31, 33 and 34 as allegedly indefinite. The basis for this rejection is the Examiner's statement that, "[c]itrate is a dicarboxylate having 4 carbons." Accordingly, the Examiner asserts that the exchange of citrate for a dicarboxylate may result in the exchange of citrate for citrate. Applicants respectfully point out that while succinate is a dicarboxylate with 4 carbons, citrate is a tricarboxylate with 6 carbons. Thus, the exchange of citrate for a dicarboxylate cannot include the exchange of citrate for citrate. Withdrawal of the indefiniteness rejection is, therefore, requested.

35 U.S.C. §102 - Anticipation

Claims 14-17, 20-23, 26, 28, 31, 33, and 34 have been rejected as allegedly anticipated under 35 U.S.C. §102(e) by US 5,561,115. In addition, claims 14-16, 18, 20-23, 28-29, 31, 33, and 34 have been rejected as allegedly anticipated under 35 U.S.C. §102(b) by US 5,372,997. Applicants respectfully invite the Examiner's attention to the §1.132 Declaration filed with this response. In his Declaration, Dr.

Teschner demonstrates the deficiencies in both the '115 and the '997 patents that are overcome in the claimed invention. Specifically, Dr. Teschner demonstrates that the '115 process results in a loss of at least 80% of the protein.

With regard to the '997 patent, Dr. Teschner points out that while some residual NaCl and NaAc may remain in the exchange column, they are not related to the '997 patent's principle of operation. As cited in MPEP §2131, "[t]he identical invention must be shown in as complete detail as is contained in the claims." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The coincidental, residual presence of certain components in the '997 method neither puts the claimed method in possession of the public, nor provides an enabling disclosure of the claimed method. In short, the '997 patent does not teach the use of NaAc to remove aluminum and does not teach the removal of citrate to prevent leakage of aluminum from glass storage containers.

35 U.S.C. §103 - Obviousness

Claims 14-18, 20-29, 31, 33 and 34 have been rejected under 35 U.S.C. §103 as allegedly obvious over US 5,561,115 or US 5,372,997 and US 5,118,794. Further, all pending claims have been rejected under 35 U.S.C. §103 as allegedly obvious over US 5,229,498 in combination with US 5,372,997.

As noted above, the '115 patent is deficient in that its method results in the loss of at least 80% of the protein, and the '997 patent does not teach the removal of citrate for removing aluminum. The Examiner has not shown that all the elements of the claimed invention are contained within the prior art, and has pointed to no teaching or motivation to combine the references in order to arrive at the claimed invention. A *prima facie* case of obviousness has, therefore, not been made. See MPEP 2143. Further, to make the proposed combination to arrive at the claimed

invention would require changing the principle of operation of the '997 patent, because it does not use the exchange of citrate to remove aluminum. Accordingly, the teachings of the references are insufficient to render the claims *prima facie* obvious. MPEP 2143.01, citing In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

With regard to the '498 patent, that reference discloses a method of exchanging multivalent metal cations (i.e., aluminum) with monovalent metal cations (i.e., sodium or potassium). The Examiner notes that, "[w]hether one obtains this cation from NaCl, or from Na acetate, or Na caprylate is not particularly relevant in the absence of evidence to the contrary." However, the claimed invention does not operate by exchange of aluminum for sodium. It operates by exchange of citrate, and citrate-bound aluminum for mono- or dicarboxylates, or their acids.

The Examiner acknowledges that removal of citrate is not taught by the references, but suggests that a citrate-free product is not required by the claims. First, applicants note that exchanging citrate is a recitation of the claims, yet the examiner does not address this. If the prior art references cited by the Examiner do not teach that element, then all claim limitations have not been taught or suggested by the references as required for a *prima facie* case of obviousness. See MPEP §2143.03, citing In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Second, the claims require that the medicament does not take up any metals when stored in a metal-containing container. The Examiner looks to the '997 patent to satisfy this element by the use of low metal-containing containers. The claimed invention, however, does not specify low metal-containing containers. Claim 14 requires that the medicament "does not take up any metals when stored in metal-containing containers." This limitation is an element of the medicament, not of the container.

The presence of citrate will cause the uptake of metals in a metal-containing container. Therefore, exchange of citrate is required in the claimed invention. As noted above, and acknowledged by the Examiner, the prior art references do not teach such a recitation.

CONCLUSION

In view of the foregoing, Applicants respectfully request the Examiner to withdraw each rejection and pass the claims to allowance. The Examiner is invited to contact the undersigned attorney to resolve any issues, in order to expedite the prosecution of the application.

June 18, 2002

Date

Respectfully submitted,



John P. Isacson

Reg. No. 33,715



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HELLER EHRMAN WHITE & McAULIFFE
1666 K Street, NW, Suite 300
Washington, DC 20006-1228
(202) 912-2000 (phone)
(202) 912-2020 (fax)

MARKED UP COPY OF AMENDED CLAIMS

16. (Amended Twice) A method as set forth in claim 14, wherein said exchanging of said citrate and optionally of said citrate-bound metals is performed using a salt of said [a carboxylic acid having] monocarboxylate, dicarboxylate, monocarboxylic or dicarboxylic acid and said monocarboxylate, dicarboxylate, monocarboxylic or dicarboxylic acid has 2 to 20 carbon atoms.



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 37966-0011

Applicant: Wolfgang TESCHNER *et al.*

Appl. No.: 09/254,288

Examiner: S. Saucier

Filing Date: April 2, 1999

Art Unit: 1651

Title: PROCESS FOR PRODUCING A PLASMA PROTEIN-CONTAINING
MEDICAMENT

DECLARATION OF WOLFGANG TESCHNER

I, Dr. Wolfgang Teschner, declare and say:

1. I am a named inventor of the subject matter claimed in United States application serial no. 09/254,288 ("the Application"). I can understand the English language.

2. I have received a Ph.D. in **biochemistry** and have worked in the field of **protein purification including plasma proteins** for 15 years. My curriculum vitae is attached as Appendix A.

3. I understand that the claimed invention is directed (I) to methods of preparing a plasma-protein-containing medicament from one of citrated plasma and a citrate-containing plasma fraction, wherein the medicament is substantially free from undesired metals and said medicament does not take up any metals when stored in metal-containing containers, and (II) to plasma-protein-containing medicaments obtainable by these

methods ("the claimed invention"). In the claimed methods, both citrate-bound metals and unbound citrate ions are exchanged for a water-soluble mono- or dicarboxylic acid under non-precipitating conditions through diafiltration, ultrafiltration or a chromatographic process.

4. I have reviewed the Office Action dated December 18, 2001, and I understand that the Examiner alleges that the claimed subject matter is disclosed in U.S. Patent Nos. 5,561,115 and 5,372,997.

5. I further understand that the basis for the Examiner's position is that the process of '115 teaches the addition of caprylate to a colloidal effluent and that the caprylate separates the colloidal solution into a (supernatant) phase containing the albumin and a disperse (colloidal) phase containing other proteins and debris.

6. In my professional opinion, however, the method taught by the '115 patent is deficient.

7. As objective evidence to support my statement in Paragraph 6, please find a Comparative Example appended hereto (Appendix B). The Example shows that in the precipitating step, using sodium caprylate as a precipitating agent at 30°C and pH 5.6, at least 80% of the protein is lost. The citrate content of the remaining supernatant is only reduced by ultra-diafiltration against a caprylate containing diafiltration buffer to a value under the detection value. In producing different albumin concentrations in the end container, different caprylate concentrations in the diafiltration buffer are used. Caprylate is only added to set the concentration in the end

container to an exact value but not for reducing citrate. Further, while salt, ethanol, and metal ions are reduced during diafiltration against water, they are not reduced to the extent according to the present invention.

8. I also understand that the basis for the Examiner's position regarding the '997 patent is that it teaches a process for removing aluminum from albumin comprising adding acetic acid (acetate) to the Cohn's fraction V, adding NaOH to the fraction, running the solution through an anion exchange column which has been washed with NaCl and equilibrated with NaAc. I further understand that while the '997 patent does not disclose the presence of citrate in the starting material, or the use of water soluble mono or dicarboxylic acids or salts thereof as exchange partners for citrate, the Examiner asserts that the presence of citrate is inherent in the Cohn's fraction V. The examiner further asserts that sodium acetate is a monocarboxylate and would therefore inherently displace citrate.

9. In my professional opinion, the '997 patent is also deficient. While citrate may be present in the fraction disclosed in the '997 patent, the specification does not disclose that the invention operates by the removal of citrate. Further, while sodium acetate may be present in the method described by the '997 patent, it is part of the buffer solution and not the means by which aluminum is removed from the albumin preparation. The principle of operation of the '997 patent is an anion exchanging group attached to an agarose or vinyl polymer bead matrix. Further, the '997 patent teaches the use of soft glass containers with low aluminum content to avoid leakage of aluminum into the solution. See Column 2, lines 17-25. But, the '997 patent does not teach the removal of citrate from the

albumin solution to avoid such leakage of aluminum from glass containers.

10. I personally supervised Ing. Sonja Svatos who performed the assay for the Comparative Example.

11. All statements made herein of my knowledge are true and all statements made on information and belief are believed to be true; and further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any document or any registration resulting therefrom.

Date: 03.06.02

Wolfgang Teschner

Dr. Wolfgang Teschner

Appendix A

CURRICULUM VITAE

Name: Wolfgang Teschner, Ph.D.

Born: May 14, 1958, Munich, Germany

Education: Diploma in Biology, University of Regensburg, Regensburg, Germany
Diploma thesis: "Investigations on folding of octopindehydrogenases"
Department of Biophysics and Physical Biochemistry
(Prof. Dr. Rainer Jaenicke)

Ph.D. University of Regensburg, Regensburg, Germany
Thesis: "Folding of octopindehydrogenase from *Pecten jacobaeus*"
Department of Biophysics and Physical Biochemistry
(Prof. Dr. Rainer Jaenicke)

Positions and

Appointments: Research Associate (3 years)
Department of Biophysics and Physical Biochemistry;
University of Regensburg,

1987-1989 Fellowship from the European Molecular Biology Organization
at the Centre National de la Recherche Scientifique, Paris, France.
Research on stability and folding of phosphofructokinase from *E. coli*,
(Prof. Dr. Jean-Renaud Garel from Institute Pasteur)

1990-1996 Member of process monitoring and process development team
(Head, Dr. Y. Linnau), Immuno AG, Vienna, Austria (after 1997, Hyland-
Immuno Division, Baxter Healthcare)

1996 – 1999 Head of process monitoring and process development "Immunoglobulines
and Albumin" Department

1999 – 2002 Head of product and process development "Immunoglobulines and
Albumin" Department

List of Publications

- Zettlmeißl,G., Teschner,W., Rudolph,R., Jaenicke,R. and Gäde,G. (1984)
Isolation, physicochemical properties, and folding of octopine dehydrogenase from *Pecten jacobaeus*. *Eur. J. Biochem.* 143, 401-407.
- Teschner, W., Rudolph,R. and Garel,J.-R. (1987) Intermediates on the folding pathway of octopine dehydrogenase from *Pecten jacobaeus*. *Biochemistry* 26, 2791-2796.
- Teschner,W. and Garel,J.-R. (1989) Intermediates on the reassociation pathway of phosphofructokinase I from *Escherichia coli*. *Biochemistry* 28, 1912-1916.
- Deville-Bonne,D., Le Bras,G., Teschner,W. and Garel,J.-R. (1989) Ordered disruption of subunit interface during stepwise reversible dissociation of *Escherichia coli* phosphofructokinase with KSCN. *Biochemistry* 28, 1917-1922.
- Le Bras,G. Teschner,W., Deville-Bonne,D. and Garel,J.-R. (1989) Urea-induced inactivation, dissociation and unfolding of the allosteric phosphofructokinase from *Escherichia coli*. *Biochemistry* 28, 6836-6841.
- Teschner,W. and Rudolph,R. (1989) A carboxypeptidase-Y-pulse method to study the accessibility of the C-terminal end during the refolding of ribonuclease. *Biochemical Journal* 260, 583-587
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- Teschner,W., Serre,M.-C. and Garel,J.-R. (1990) Enzymatic properties, renaturation and metabolic role of mannitol-1-phosphate dehydrogenase from *Escherichia coli*, *Biochimie* 72, 33-40.
- Serre,M.-C. Teschner,W. and Garel,J.-R. (1990) Specific suppression of heterotropic interactions in phosphofructokinase by the mutation of leucine 178 into tryptophan. *The Journal of Biological Chemistry* 265, 12146-12148.
- Teschner,W., Serre,M.-C. and Garel,J.-R. (1990) Introduction by site-directed mutagenesis of a tryptophan residue as a fluorescent probe for the folding of *Escherichia coli* phosphofructokinase. *Biochimie* 72, 403-406.
- Muchitsch,E.-M., Teschner,W., Linnau,Y. and Pichler,L. (1996) In vivo effect of α -1-acid glycoprotein on experimentally enhanced capillary permeability in guinea-pig skin. *Archives internationales de Pharmacodynamie et de Therapie* 331,3,313-321.

APPENDIX B

Serial No. 09/254288

Comparative Example

Production of IV-1-supernatant from II-supernatant.

The experiment started with Cohn Fraction II supernatant and followed the protocol set forth in Example 1 of U.S. Patent No. 5,561,115 (identical to Example 1 of EP 0 696 595 A1).

The specifications of the Cohn Fraction II supernatant were as follows:

Lot: A16498

Protein: 2.46%

Volume: 1500 ml

pH: 7.70

Temp: -2.7°C

Ethanol: 25%

1. WF1 was added to the Cohn Fraction II supernatant at a concentration of 311 ml/l (467 ml), at a temperature of -5° to -6°C.
2. The following reagents were added in the stated amounts (concentrations):
 - 112.5 ml of WF1 (75 ml/l of CF-II supernatant)
 - 1.91 g of sodium acetate*3H₂O (1.275 g/l of CF-II supernatant)
 - 4.05 ml of acetic acid (2.7 ml/l of CF-II supernatant)

The pH for this step should be between 5.1 and 5.15; pH_{actual} was 5.13 / -3.9°C. The solution was stirred over night at -5° to -6°C, then centrifuged at -5°C for 30 min at 4600 rpm.

3. The precipitate is dissolved 1+5 in 0.9% NaCl in order to determine protein concentration.

sample	weight (g)	V (ml)	protein (%)
IV-1-supernatant		2020	1.65
IV-1-precipitate	30.3	165	0.91

20 ml of sample

4. According to the '115 protocol, sodium caprylate was added to Cohn fraction IV-1 effluent, which insolubilized alpha and beta globulins by wetting, or partitioning albumin from these unwanted proteins. Sodium caprylate also functions as an antiviral agent, and additionally permits mechanical separation of albumin.

10 grams of sodium caprylate per liter was added to fraction IV-1 supernatant (20g), which was heated to 30°C while simultaneously adjusting solution pH from 6.02 / 11.0 °C to about 5.6/11.3°C with concentrated acetic acid. The solution was allowed to stir for > 6 hours at 30 °C, during which the pH was maintained at about 5.3 to 5.6, but preferably at 5.4

5. The sodium caprylate-treated solution was then cooled to 18°C to inhibit bacterial growth, and centrifuged. Then, 1 gram of DEAE-Sephadex A50 was added to the centrifugation supernatant, and stirred for 1 hour at room temperature, to aid filtration. The centrifugation precipitate was insoluble in 0.9% NaCl.

sample	weight (g)	V (ml)	protein (%)
Centr. supernatant		1770	0.35
Centr precipitate	133.5		

20 ml of sample

6. The caprylate supernatant was then clarified through Cuno 90SA filters, which produced the DEAE filtrate. The filters were pre-rinsed with 432 ml of WF1. The resulting filtrate pH was then increased to neutrality (6.8 to 7.2) with sodium carbonate.

sample	V (ml)	protein (%)
DEAE-filtrate	1730	0.35

20 ml of sample

7. The DEAE-Sephadex clarified filtrate was then ultrafiltered with 30K Regenerated Cellulose (UF:PLCTK30 50 cm² Lot P8AM1450-19) (regenerated cellulose membranes support the removal of aluminium) and diafiltered against at least seven volume exchanges of sodium caprylate diafiltration buffer to remove metal contaminants, ethanol and salts. The filtrate was concentrated to 15% protein (40 ml), then diafiltration was continued against 16 mM sodium caprylate to a final protein concentration of 20% (30 ml).

sample	V (ml)	protein (%)
diaconcentration	34.0	14.08
rinsing	17.5	4.31

8. Finally, the concentrate is sterile filtered over Millex 0.22 µm.

Protein balance:

sample	V (ml)	v (ml) corr.	protein (%)	protein (g)	yield (%)
IV-I-supernatant	2020	2020	1.65	33.33	100.0
centr. supernatant	1770	1788	0.35	6.26	18.8
DEAE filtrate	1730	1768	0.35	6.19	18.6
diaconcentration	34.0	35	14.08	4.95	14.9
rinsing	17.5	18	4.31	0.78	2.3

Citrate results

sample	V (ml) corr.	protein (g)	citrate mmol/l
IV-I-supernatant	2020	33.33	8.05
centr. supernatant	1788	6.26	8.93
DEAE filtrate	1768	6.19	8.65
diaconcentration	35	4.95	<0.10
rinsing	18	0.78	0.10

Although citrate is decreased during diafiltration to values <0.10 mmol/l, the method is of no use because in the previous precipitating step (with caprylate as precipitating agent) at least 80% of the protein is lost.